UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

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Subject: Response to Public Comments Received on the Draft Aldicarb Human Health Risk Assessment

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Comments to the Draft Aldicarb Risk Assessment were received from AgLogic Chemical, LLC, Office of Pest Management Policy, United States Department of Agriculture (USDA) and Earthjustice concerning the draft human health risk assessment. Below please find a summation of comments and the Health Effects Division (HED) responses.

1) **Commenter:** Dr. Antoine Puech, AgLogic Chemical, LLC

Comment: As described in MRID 50013101, AgLogic Chemical was able to reproduce the results of the aldicarb dietary assessment for the food only assessment, reporting utilization of about 65% of the aPAD for children 1-2 years old, the highest exposed population subgroup. A second assessment was conducted assuming that no residues of aldicarb occur in imported potatoes, oranges or orange juice based on information indicating that virtually all imported potatoes, oranges and orange juice come into the US from countries that have banned aldicarb, or come from countries where aldicarb is not registered. In addition, the percent crop treated (PCT) value for sweet potato was set at 35%, since sweet potato use in the U.S. is restricted to Louisiana and Mississippi. These refinements resulted in a reduced risk estimate of 27% of the aPAD for children 1-2 years old. Finally, a third dietary assessment reflecting food and water exposures was conducted making use of an estimated drinking water concentration (EDWC) of 0.59 ppb, as determined for ground water by AgLogic. This assessment resulted in an estimated risk of 64% aPAD for children 1-2 years old, the most highly exposed population subgroup.

HED Response: HED acknowledges receipt of the information from AgLogic refining the PCT estimates for sweet potato, potato, and orange; as well as the modeling assumptions recommended for drinking water. Based on the submitted comments, HED is coordinating with the Biological and Economic Analysis Division (BEAD) to determine the appropriate PCT values for sweet potatoes, and for imported potatoes and oranges. If there is no significant use of aldicarb in countries exporting potatoes and citrus to the United States, as stated by the commenter, HED recommends that aldicarb tolerances be revoked for those commodities since there would no longer be a need for them. Revisions to the drinking water residues are being considered by the Environmental Fate and Effects Division (EFED).

2) **Commenter:** Dr. Sheryl H. Kunickis, Director, Office of Pest Management Policy, USDA

Comment: USDA supports the continued registrations of aldicarb in view of its benefits to U.S. agriculture. A number of suggestions for refinement of the risk assessments were provided for food, drinking water, surface water and groundwater. For the dietary assessment, suggested refinements focus primarily on lowering the percent crop treated estimates, especially for imported commodities as aldicarb use has been banned in Mexico, Brazil, the EU and a number of South American and Caribbean countries. Estimates on the percent of imported potatoes, frozen potatoes and citrus (orange, limes) treated with aldicarb can be expected to decrease. Additionally, Pesticide Data Program (PDP) results generally show no detectable residues of aldicarb or aldicarb sulfone in analyzed crop or water samples.

HED Response: HED is coordinating with the Biological and Economic Analysis Division (BEAD) to determine the appropriate PCT values for sweet potatoes, and for imported potatoes and oranges, considering the information provided by the commenter. If percent crop treated decreases over time as stated by the commenter, this information will be incorporated into Agency risk assessments. PDP results are used as appropriate in the dietary risk assessment.

3) **Commenter:** Matt R. Baca, Earthjustice

Comment: A total of 76 files were submitted by Matt R. Baca of Earthjustice on behalf of clients, Natural Resources Defense Council (NRDC), Pesticide Action Network (PAN), Farmworker Justice, United Farm Workers (UFW), Pineros y Campesinos Unidos del Noroeste (PCUN) and California Rural Legal Assistance Foundation.

HED Response: Of the 76 files submitted by Earthjustice, 75 files were references from a document titled "Farmworker and Conservation Comments on One Carbamate and Three Organophosphate Pesticides", which was the 76th file. The focus of each response has been grouped and comments made below as appropriate.

HED Response to "EPA Should Revoke All Tolerances Because of Unacceptable Food and Drinking Water Risks":

The dietary assessment conducted for food only results in exposure estimates below the level of concern for the general population and all population subgroups. Dietary assessments considering drinking water result in exposure estimates above the level of concern. The final dietary assessment will consider active US registrations, import tolerances, percent of crop treated and imported, and estimates of concentrations in drinking water provided by the Environmental Fate and Effects Division (EFED). Health Effects Division (HED) defers to Pesticide Re-Evaluation Division (PRD) on the decision to revoke tolerances.

HED Response to "EPA Must Revoke All Tolerances and Cancel All Uses to Prevent Neurodevelopmental Harm to Children":

There is no comment on aldicarb or the carbamates as a class under this title. No response necessary.

HED Response to "EPA Fails to Account Fully for Other Critical Health Risks":

Regarding the question of mutagenicity, Earth Justice cites a 1986 study by Rashid and Mumma in which aldicarb is reported to cause irreversible damage to the DNA of *Salmonella typhimurium* bacterial models, suggesting that aldicarb may be genotoxic.

Only an abstract of the paper was located, which contained very limited information. The study authors reported that aldicarb at 1000 µg caused DNA damage in *S. typhimurium* TA1538, which is deficient in the uvrB repair mechanism vs. strain TA 1978, the repair proficient strain (wild type $uvrA^+$). No further information was provided. Based on the paucity of data, the Agency determined that it was impossible to assess the quality and/or the relevance of the data. Using a weight-of-the-evidence (WOE) approach, which is typically employed when conflicting results are found in databases (Dearfield *et al.*, Mutat Res 521:121-135, 2002), the Agency points out that aldicarb was not genotoxic in other bacterial DNA repair test systems and did not cause unscheduled DNA damage in primary rat hepatocytes. Furthermore, damage to DNA alone is not sufficient to cause a concern because damage can be repaired by a multitude of repair processes. For aldicarb, this is illustrated by the negative results for mammalian cell gene mutations and chromosome aberrations in acceptable guideline studies.

Regarding the epidemiology data, the Agency has assessed the 2007 study cited by Earth Justice regarding colon cancer. Overall, the authors of the study note the significance of the finding, but suggest caution due to small numbers, the role of chance, and lack of biological explanation.

HED Response to "EPA's Model Does Not Protect Bystanders and Farmworkers from Drift, Dust, Take-Home Exposures and Volatilization & The Assessments Reveal Unacceptable Risks to Farmworkers that Must Be Prevented and Underestimate the Extent of the Risks":

Spray drift is recognized as a potential source of exposure to individuals nearby pesticide applications, and where appropriate, will be quantitatively evaluated by HED. However, aldicarb applications are unlikely to result in spray drift because the end use product is formulated as a granular and is incorporated into the soil. Additionally, an air monitoring study (i.e., also known as field volatility) is available for aldicarb (*Report for the Application and Ambient Air Monitoring of Aldicarb. California Environmental Protection Agency Air Resources Board. November 16, 1998* http://www.cdpr.ca.gov/docs/emon/pubs/tac/tacpdfs/aldicarb.pdf). A total of 115 ambient air samples were collected from two counties within California. All samples were found to be less than the limit of detection (LOD) of 0.050 µg/sample. Therefore, quantitative spray drift and volatilization assessments have not been conducted for aldicarb.

HED does not believe there is significant exposure from track-in of aldicarb based on the registered use pattern. Aldicarb is formulated as a granular product that is soil incorporated. HED notes that none of the references provided for house dust provide specific information on aldicarb in house dust. HED does not believe there is significant post-application exposure to farm workers based on the use pattern of aldicarb (soil incorporated granular) and there is limited potential for worker dermal exposure to soil incorporated pesticides.

The registered product for aldicarb is a restricted use pesticide (RUP) and, as such, may only be purchased and used by certified applicators or person under their direct supervision. As an RUP, the aldicarb label contains substantial protective measures to prevent worker exposure. Aldicarb handlers must either use a closed loading system or use extensive Personal Protective Equipment (PPE) (e.g., chemical resistant gloves, protective eyewear, chemical-resistant apron, and a respirator). HED's assessment is reflective of potential exposure and risks to workers from the use of aldicarb, while wearing required PPE or using closed loading systems. Furthermore, the revised Worker Protection Standard now includes a minimum age requirement of 18 years for handling pesticides.

HED Response to "EPA Must Protect Against Environmental Justice Impacts":

Potential areas of environmental justice concerns, to the extent possible, were considered in the aldicarb draft human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations" (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, Office of Pesticide Programs (OPP) considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home

that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups, and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures are evaluated, based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

EPA is monitoring reported aldicarb human health incidents. EPA recently posted an updated review of all reported aldicarb human health incidents. This document is entitled "Aldicarb: Tier I Update of Human Incidents for Draft Risk Assessment" (E. Evans, # D430435) and can be found the Aldicarb Docket, #EPA-HQ-OPP-2012-0161-0024. The aldicarb incident memo states, "The review finds that there is a low frequency and generally low severity of aldicarb incidents". This incident report includes a review of SENSOR-Pesticides data from 1998-2011. A review of aldicarb case reports in the Sentinel Event Notification System for Occupational Risks (SENSOR)-Pesticides database from 2012-2013 identifies a total of four additional cases; three of which involve exposure to the illegal product "Tres Pasitos", including two intentional self-harm cases and one case involving an accidental exposure from cleaning a contaminated room. The fourth case involved the accidental ingestion of Temik that was kept in a 7-up bottle. Of these four additional cases, two were low severity and two (ingestions) were moderate in severity. EPA participates in the SENSOR-Pesticides program and routinely reviews this database to inform human health risk assessments. EPA involvement with SENSOR-Pesticides includes close collaboration and incident data sharing with partners at National Institute for Occupational Safety and Health (NIOSH) and participating states including both California and Washington.

HED Response to "EPA Must Conduct a Cumulative Organophosphate Risk Assessment and Assess Cumulative Risk Associated with Organophosphate-Carbamate Mixtures":

Aldicarb is a member of the *N*-methyl carbamate (NMC) class of pesticides. Like other NMCs, the initiating event in the adverse outcome pathway (AOP)/mode of action (MOA) for aldicarb involves inhibition of the enzyme acetylcholinesterase *via* carbamylation of the serine hydroxyl group located in the active site of the enzyme. This inhibition leads to accumulation of acetylcholine and ultimately to neurotoxicity in the central and/or peripheral nervous system. This MOA is similar to the organophosphate (OP) class of chemicals, as they both result in inhibition of the acetylcholinesterase enzyme. However, they are differentiated by their action upon the active site of the enzyme, which results in clear differences in the timing and duration of inhibition between the two classes.

In the OP MOA, inhibition of acetylcholinesterase occurs *via* phosphorylation, as opposed to carbamylation with NMCs. Phosphorylation results in an irreversible binding and a permanent inhibition of the bound enzyme. Inhibition occurs within a few hours and continues until new,

uninhibited enzymes are produced. This results in the OPs exhibiting a phenomenon known as steady-state cholinesterase inhibition. After repeated dosing with an OP at the same dose level, the degree of cholinesterase inhibition comes into equilibrium with the production of new, uninhibited enzyme. At this point, the amount of AChEI at a given dose remains consistent across duration. The NMCs react differently in that carbamylation of the serine hydroxyl group results in a reversible binding process thus allowing for rapid reactivation of the enzyme. The NMCs, therefore, have a unique mode of action that results in rapid onset and recovery of the enzyme.

EPA participated in a workgroup by the International Life Sciences Institute (ILSI) to discuss issues surrounding common mechanism as it applies to the organophosphate pesticides. The ILSI workgroup recommended that the organophosphates be classified as a common mechanism group. EPA accepted this recommendation (Common Mechanism of Toxicity: A Case Study of Organophosphorus Pesticides, Toxicological Sciences, 41:8-20 (1998)). In addition, EPA has consulted the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) regarding, "Identifying Carbamate Pesticides that Have a Common Mechanism of Toxicity" (https://archive.epa.gov/scipoly/sap/meetings/web/pdf/finalrpt-2.pdf). This meeting addressed the key question: Should carbamates and OP pesticides be considered a single common mechanism group? The meeting concluded, "It would be a mistake to apply the cumulative risk umbrella to chemical classes of agents per se; rather one should apply it to all agents that act through the common mechanism". The mechanism of carbamates differs from OPs in that they carbamylate the enzyme and create a short-lived reaction. This difference in mechanism does not allow for cumulative risks to be assessed for OPs and carbamates. The decision to place carbamates into a common mechanism group was released for public comment in 2001. Since this time, there has been no new information regarding the mechanisms for either OPs or carbamates that would warrant reconsideration of this decision.

HED Response to "EPA Cannot Use an Intentional Human Dosing Study to Reduce Protections for Aldicarb":

This human study was reviewed by EPA's Human Studies Review Board (HSRB), as required by EPA's Human Subjects Protections rule, 40 CFR Part 26 (effective April 7, 2006), who concluded that use of the human study endpoint was appropriate for human health risk assessment. Because these human data are considered reliable, and the study is considered scientifically valid, the human study is regarded as the most suitable for this single-chemical risk assessment. It is to be noted that Earth Justice does not discuss how the study is ethically deficient or scientifically unsound. The study conformed to the standards in effect at the time it was performed, and it would not be discarded or the findings considered invalid due to the revision of regulations regarding such testing. From the HSRB report, regarding Scientific Considerations, HSRB concluded that the cholinesterase data from the aldicarb human study were reliable. Regarding Ethical Considerations, the HSRB concluded that, although the aldicarb human toxicity study failed to fully meet the specific ethical standards prevalent at the time the research was conducted, there was no clear and convincing evidence that the research was fundamentally unethical; i.e., intended to seriously harm participants or that informed consent was not obtained. Additionally, there was no clear and convincing evidence of significant deficiencies in the ethical procedures that could have resulted in serious harm (based

on the knowledge available at the time the study was conducted), nor that information provided to participants seriously impaired their informed consent.